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(12) UK Patent Application (19) GB (11) 2 357 762 (13) A

(43) Date of A Publication 04.07.2001

(21) Application No 0105982.3

(22) Date of Filing 12.03.2001

(30) Priority Data
(31) 200000402 (32) 13.03.2000 (33) DK
(31) DK0000183 (32) 13.04.2000 (33) WO

(71) Applicant(s)
H Lundbeck A/S
(Incorporated in Denmark)
9 Ottiliavej, DK-2500 Valby, Copenhagen, Denmark

(72) Inventor(s)
Hans Peterson
Klaus Peter Bogeso
Per Holm

(74) Agent and/or Address for Service
Stevens Hewlett & Perkins
1 St Augustine's Place, BRISTOL, BS1 4UD,
United Kingdom

(51) INT CL[7]
C07D 307/88 , A61K 31/34 , A61P 25/24

(52) UK CL (Edition S)
C2C CNB CVN C1474 C213 C22Y C220 C25Y C253 C29X
C29Y C31Y C311 C32Y C326 C43X C62Y C620 C650
C676 C697 C80Y C802
U1S S2417

(56) Documents Cited
EP 0347066 A1

(58) Field of Search
UK CL (Edition R) C2C CNB
INT CL[6] C07D 307/88
DATA-BASE : CAS-ON-LINE

(54) Abstract Title
Preparation of Crystalline Base or Salts of Citalopram

(57) The present invention relates to the crystalline base of the antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile, formulations of said base, a process for the preparation of purified salts of citalopram, such as the hydrobromide, using the base, the salts obtained by said process and formulations containing such salts.

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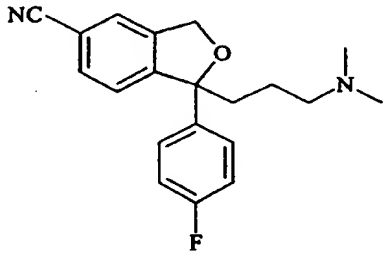
Crystalline Base of Citalopram

The present invention relates to the crystalline base of the well known antidepressant drug citalopram,1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile, formulations of said base, a process for the preparation of purified salts of citalopram, such as the hydrobromide, using the base, the salts obtained by said process and formulations containing such salts.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



(I)

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75* , 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method, which may be used for preparing citalopram. The citalopram prepared was isolated as the oxalate, the hydrobromide and the hydrochloride salt, respectively. Furthermore, the citalopram base was obtained as an oil (B.P. 175 C/0.03 mmHg). Citalopram is marketed as the hydrobromide and the hydrochloride, respectively.

A number of processes for the preparation of citalopram have been disclosed. In many of these, the last step of the process is a conversion of a group different from cyano in the 5 position of the direct analogue of citalopram to a 5-cyano group. So citalopram has been prepared by:

Exchange of 5-halogen, or 5-CF_3-$(CF_2)_n$-SO_2-O- with cyano (DE 2,657,013 and co-pending WO 0011926 and WO 0013648)

Conversion of a 5-amido or 5-ester group to a 5-cyano group (WO 9819513)

Conversion of a 5-amino group to a 5-cyano group (WO 9819512)

Conversion of a 5-formyl group to a 5-cyano group (WO 9900548)

Conversion of a 5-oxazolinyl or 5-thiazolinyl group to a 5-cyano group (WO 0023431)

Other processes for the preparation of citalopram comprise exchange of the 5-bromo group of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide with 5-cyano followed by alkylation with a 3-(N,N-dimethylamino)propyl-halogenide (DE 2,657,013 and WO 9819511).

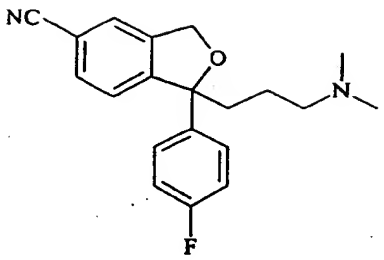
Many of the processes mentioned above have the disadvantage that it is difficult to separate the intermediates formed during the process (the intermediates mentioned above or earlier intermediates) from the end product and, accordingly, extensive purification procedures involving loss of citalopram are required in order to obtain the necessary quality of the end product.

It has now been found that the base of citalopram may be obtained as a very nice and pure crystalline product, which may easily be handled and conveniently be formulated into tablets and other pharmaceutical forms. Furthermore, it has surprisingly been found that a very good and efficient purification of citalopram may be obtained during manufacture of citalopram (e.g. of the hydrobromide or the hydrochloride salt) by crystallising the base, and thereafter optionally forming a salt from the base.

This purification process is particularly useful for removing intermediates which are structurally closely related to citalopram, in particular compounds which only differ from citalopram by the substituent situated in position 5 on the isobenzofurane ring, and intermediates which have physical/chemical properties which are close to those of citalopram, e.g. the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuranes having halogen (in particular bromide and chloride), an amide or an ester in position 5 of the isobenzofurane ring, or 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide, or -cloride.

Summary of the invention

The present invention provides the crystalline base of the compound



(I)

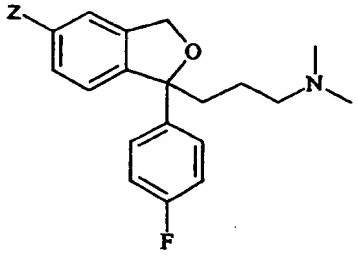
In a second aspect, the invention provides a process for the manufacture of a salt of citalopram, preferably the hydrobromide or hydrochloride in which the free base of citalopram is precipitated in crystalline form, optionally re-crystallised one or more times and then transferred to a pharmaceutically acceptable salt of citalopram.

In a further aspect, the invention relates to the pure crystalline salt, preferably the hydrobromide or hydrochloride prepared by the process of the invention.

In particular, the invention relates to a process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt thereof.

In particular, the invention relates to a process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or crude mixture of citalopram.

More particularly, the present invention relates to a process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



(II)

wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, -CHO, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of

citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.

The crude mixture of citalopram containing the compound of formula II as an impurity may be prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source, or by subjecting 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranhalogenide, in particular the bromide, to a cyanide exchange reaction followed by alkylation with a 3-(N,N-dimethylamino)propyl-halogenide.

In a particular embodiment of the invention, Z is halogen, in particular bromide or chloride.

In a particularly preferred embodiment of the invention, the salt prepared is the hydrobromide or hydrochloride salt of citalopram.

The crude salt may be any convenient salt, such as the hydrobromide, hydrochloride, sulphate, oxalate, phosphate, nitrate or any other convenient salt. Other salts are salts of organic acids.

In a preferred embodiment of the invention, the crude salt is the sulphate, the hydrobromide or the hydrochloride salt.

The invention also relates to a hydrochloride or hydrobromide salt of citalopram prepared by the processes of the invention. In particular, the invention relates to a hydrochloride or hydrobromide salt of citalopram having a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

In yet another aspect, a pharmaceutical formulation of the free base of citalopram, or a hydrobromide or hydrochloride prepared from said base, is provided. Preferably the formulation is for oral administration.

The formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

In particular, the pharmaceutical composition of the invention contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

The crystalline base of citalopram is preferably more than 99.8% w/w pure, most preferably more than 99.9% w/w pure (peak area). The melting point is preferably a range within 90 – 93 °C, most

preferably 91 - 92 °C (DSC; onset, open capsule) or it is between 92 and 94°C, preferably 92.5 and 93.5 °C (DSC; onset, closed capsule). The crystalline base of citalopram is preferably in racemic form.

The terms "crude salt" and "crude mixture" refer to the fact that the salt and the mixture, respectively, comprise impurities, in particular impurities of formula II, which must be removed or which it is desired to remove.

The crude salt may be a salt separated directly from the reaction mixture, or the crude reaction mixture may have been subjected to some initial purification, e.g. one re-crystallisation, and /or treatment with activated carbon or silica gel, and the salt formed subsequently by treatment with an acid using methods known in the art. The salt may be isolated by precipitation or it may exist in a solvent, e.g. in the mixture resulting directly from the synthesis of the salt.

Similarly, the crude mixture comprising citalopram may be obtained directly from the synthesis of the compound according to any of the above mentioned processes or it may have been subjected to some initial or simultaneous purification, e.g. one re-crystallisation, treatment with activated carbon or silica gel.

The base of citalopram may be set free from the crude salt by dissolving the crude salt in a mixture of water and an organic solvent and then adding a base. The organic solvent may be toluene, ethyl acetate or any other suitable solvent and the base may be any convenient base, preferably NaOH or NH_3. Likewise, the base of citalopram may, if necessary, be set free from a crude mixture containing citalopram by treatment with a base.

Crude mixtures containing citalopram base may be subjected to further purification and extraction, before the base is precipitated in crystalline form. The base of citalopram may be isolated by separation of the organic phase, evaporation of the solvent in order to obtain the base most probably as an oil and then crystallisation of the base from an aprotic solvent, such as an alkane, including n-heptane, hexane and isooctane, and high and low boiling petroleum ethers and substituted aromates, incl toluene and xylenes. Crystalline citalopram base may be re-crystallised from the same solvents.

The pharmaceutically acceptable salt of citalopram, such as the hydrobromide or hydrochloride, may be prepared by methods known in the art. So, the base may be reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously. The

hydrobromide or hydrochloride of citalopram obtained by the method of the invention has a very high purity, preferably more than 99,8% pure, most preferably more than 99,9 % purity. Other salts of citalopram, e.g. the oxalate, may also be obtained in a very pure form by this process.

The cyanide exchange reactions mentioned above may be carried out as described in the patent applications mentioned above.

In particular, when Z is halogen, or CF_3-$(CF_2)_n$-SO_2-O- wherein n is an integer in the range 0-8, incl., the conversion to a cyano group may be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, $Zn(CN)_2$ or $(R^4)_4NCN$ where R^4 indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a palladium catalyst and a catalytic amount of Cu^+ or Zn^{2+}, or with $Zn(CN)_2$ in the presence of a palladium catalyst.

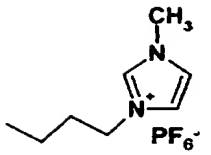
The cyanide source is used in a stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material. R^4N^+ may conveniently be $(Bu)_4N^+$. The cyanide compound is preferably NaCN or KCN or $Zn(CN)_2$.

The palladium catalyst may be any suitable Pd(0) or Pd(II) containing catalyst, such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh)_2Cl_2$, etc. The Pd catalyst is conveniently used in an amount of 1-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 %. Conveniently, about ½ eq. is used per eq. Pd . Any convenient source of Cu^+ and Zn^{++} may be used. Cu^+ is preferably used in the form of CuI and Zn^{2+} is conveniently used as the $Zn(CN)_2$ salt.

When Z is Br or I, the conversion to a cyano group may also be carried out by reaction with Cu(CN) without catalyst. In a preferred embodiment, the reaction is performed at elevated temperature.

In another aspect of the invention, the reaction is performed in an ionic liquid of the general formula $(R^5)_4N^+$, X^-, wherein R^5 are alkyl-groups or two of the R^5groups together form a ring and X^- is the counterion. In one embodiment of the invention, $(R^5)_4N^+X^-$ represents



In another particular aspect, the reaction is conducted with apolar solvents such as benzene, xylene or mesitylene and under the influence of microwaves by using *i.e.* Synthewave 1000™ by Prolabo. In a particular aspect, the reaction is performed without added solvent.

The temperature ranges are dependent upon the reaction type. If no catalyst is present, preferred temperatures are in the range of 100-200°C. However, when the reaction is conducted under the influence of microwaves, the temperature in the reaction mixture may raise to above 300 °C. More preferred temperature ranges are between 120-170°C. The most preferred range is 130-150°C. If catalyst is present, the preferred temperature range is between 0 and 100°C. More preferred are temperature ranges of 40-90°C. Most preferred temperature ranges are between 60-90°C.

Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

When Z is Cl or Br, the conversion to a cyano group may also be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, $Zn(CN)_2$ or $(R^4)_4NCN$ where $(R^4)_4$ indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a nickel catalyst.

The nickel catalyst may be any suitable Ni(0) or Ni(II) containing complex which acts as a catalyst, such as $Ni(PPh_3)_3$, (σ-aryl)-$Ni(PPh_3)_2Cl$, etc. The nickel catalysts and their preparation are described in WO 96/11906, EP-A-613720 or EP-A-384392.

In one embodiment of the invention, the reaction is carried out in the presence of a catalytic amount of Cu^+ or Zn^{2+} .

In a particularly preferred embodiment, a Nickel(0) complex is prepared *in situ* before the cyanation reaction by reduction of a Nickel(II) precursor such as $NiCl_2$ or $NiBr_2$ by a metal, such as zinc, magnesium or mangan in the presence of excess of complex ligands, preferably triphenylphosphin.

The Ni-catalyst is conveniently used in an amount of 0.5-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, mean substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 %. Any convenient source of Cu^+ and Zn^{2+} may be used. Cu^+ is preferably used in the form of CuI and Zn^{2+} is conveniently used as the $Zn(CN)_2$ salt or formed in situ by reduction of a Nickel (II) compounds using zinc.

The Ni catalysts are *i.e.* Ni (0), Pd(0) or Pd(II) catalysts as described by Sakakibara et. al. in Bull. Chem. Soc. Jpn., **61**, 1985-1990, (1988). Preferred catalysts are $Ni(PPh_3)_3$ or $Pd(PPh_3)_4$, or $Pd(PPh)_2Cl_2$.

The reactions may be performed in any convenient solvent as described in Sakakibara et. al. in Bull. Chem. Soc. Jpn., **61**, 1985-1990, (1988). Preferred solvents are acetonitril, ethylacetat, THF, DMF or NMP.

When Z is CHO, the conversion to a cyano group may be carried out by conversion of the formyl group to an oxime or similar group by reaction with a reagent R^6-V-NH_2 wherein R^6 is hydrogen, optionally substituted alkyl, aryl or heteroaryl and V is O, N or S, followed by dehydration with a common dehydrating agent, for example thionylchloride, acetic anhydride/pyridine, pyridine/HCl or phosphor pentachloride. Preferred reagents R^6-V-NH_2 are hydroxylamin and compounds wherein R^6 is alkyl or aryl and V is N or O.

When Z is -COOH, the conversion to a cyano group may be carried out via the corresponding acid chloride, ester or amide.

The acid chloride is conveniently obtained by treatment of the acid with $POCl_3$, PCl_5 or $SOCl_2$ neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of N,N-dimethylformamide. The ester is obtained by treatment of the acid with an alcohol, in the presence of an acid, preferably a mineral acid or a Lewis acid, such as HCl, H_2SO_4, $POCl_3$, PCl_5 or $SOCl_2$. Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol. The ester or the acid chloride is then converted to an amide or by amidation with ammonia or an alkylamine, preferably t-butyl amine.

The conversion to amide may also be obtained by reaction of the ester with ammonia or an alkylamine under pressure and heating.

The amide group is then converted to a cyano group by dehydration. The dehydrating agent may be any suitable dehydrating agent, and the optimal agent may easily be determined by a person skilled in the art. Examples of suitable dehydrating agents are $SOCl_2$, $POCl_3$ and PCl_5, preferably $SOCl_2$.

In a particularly preferred embodiment, the carboxylic acid is reacted with an alcohol, preferably ethanol, in the presence of $POCl_3$, in order to obtain the corresponding ester, which is then reacted with ammonia thereby giving the corresponding amide, which in turn is reacted with $SOCl_2$ in toluene comprising a catalytic amount of N,N-dimethylformamide.

Alternatively, a compound where Z is –COOH may be reacted with chlorosulfonyl isocyanate in order to form the nitrile, or treated with a dehydrating agent and a sulfonamide.

When Z is $-NHR^1$, where R^1 is hydrogen, the conversion into cyano is preferably performed by diazotation and followed by reaction with CN^-. Most preferably $NaNO_2$ and CuCN and/or NaCN are used. When R^1 is alkylcarbonyl, it is initially subjected to hydrolysis thereby obtaining the corresponding compound wherein R^1 is H which is the converted as described above. The hydrolysis may be performed either in acidic or basic environment.

The compounds of formula (II) may be prepared as described in DE 2,657,013, WO 0011926 and WO 0013648, WO 9819513, WO 9819512 and WO 9900548.

Throughout this specification with claims halogen means chloro, bromo or iodo.

The term alkyl refers to a branched or unbranched alkyl group, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, and 2-methyl-1-propyl.

The term aryl refers to a carbocyclic aromatic group, in particular phenyl. Aralkyl refers to an arylalkyl group wherein aryl and alkyl is as defined above. The aryl and aralkyl groups may optionally be substituted, e.g. with alkyl groups, forming for example tolyl.

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection. Preferably the pharmaceutical compositions of the invention are administered orally.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

In particular, the formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

According to the present invention, the base of citalopram has been found to be crystalline with stable and nice white crystals and it has been found that the base may easily be crystallised in a very pure form. So for example more than 99.8% w/w pure citalopram base was obtained by crystallisation from up to 95% pure hydrobromide without further purification. Accordingly, the process of the invention for preparing salts of citalopram has been found to give the salts as very pure products of pharmaceutically acceptable quality. Accordingly, the yield may be improved substantially during the manufacture of citalopram.

Finally, it has been found that the crystalline citalopram base may be formulated into very good and stable solid formulations with good release properties.

The invention is further illustrated by the following examples.

Example 1

Crystallisation of R,S-Citalopram as the free base.

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile.

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile hydrobromide (101 grams, 0.25 mole) prepared from 1-(3-Dimethylaminopropyl)- 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide, is suspended in water (500 ml) and toluene (500 ml). NaOH (60 ml, 5 N (aq)) is added and the mixture (pH>10) is stirred for 15 min. before the phases are separated. The organic phase is washed with water (2x100 ml) and filtered through a pad of filter help. The volatiles are removed *in vacuo* and the title compound is obtained as an oil. n-Heptane (400 ml) is added and the mixture is heated to 70 °C. On cooling, crystals form. The white crystals of the title compound are filtered off and dried at ambient temperature over night in vacuo. Yield: 75.4 grams (93%). DSC(onset, open capsule): 91.3-91.8 °C DSC (onset, closed capsule): 92.8 °C. Purity: (> 99.8 % (peak area)).

Anal. calcd. for C20H21N2F1O1; C, 74.04; H, 6.54; N, 8.64. Found C, 74.01; H, 6.49; N, 8.59. 1H-NMR (DMSO-d6 , 500 MHz): 1.21 (1H, m), 1.29 (1H, m), 2.02 (6H, s), 2.09-2.23 (4 H, m), 5.15 (1H, d J=12.5 Hz), 5.22 (1H, d J=12.5 Hz), 7.16 (2H, t J=8.5 Hz), 7.60 (2H, dt J=8.5 Hz J=1.2 Hz), 7.76 (1H, d J= 8.5 Hz), 7.79 (1H, d J=8.5 Hz), 7.80 (1H, s). 13C-NMR (DMSO-d6 , 125 MHz): 21.8, 38.3, 45.0, 58.8, 71.0, 90.7, 110.5, 115.1 (d J=22 Hz), 118.8, 123.1, 125.1, 127.0 (d J=8 Hz), 132.0, 140.0 (d J=3 Hz), 140.5, 149.5, 161.3 (d J=245Hz).

Example 2

a) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene is evaporated and the citalopram base obtained is dissolved in n-heptane at elevated temperature. The very pure free base of citalopram is precipitated by cooling.

b) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene is evaporated and the citalopram base obtained is dissolved in methanol. The mixture is treated with activated carbon and filtrated and the solvent is evaporated. The purified free base is dissolved in n-heptane at elevated temperature. Then the very pure free base of citalopram is precipitated by cooling.

c) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene phase is treated with silicagel, the toluene is evaporated and the citalopram base obtained is dissolved in n-heptane at elevated temperature. The very pure free base of citalopram is precipitated by cooling.

d) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene phase is treated with silicagel, the toluene is evaporated and the citalopram base obtained is dissolved in methanol. The mixture is treated with activated carbon and filtrated and the solvent is evaporated. The purified free base is dissolved in n-heptane at elevated temperature. Then the extremely pure free base of citalopram is precipitated by cooling.

Example 3

Wet granulation and preparation of tablets

The batch size was 200 g and the granulation was performed in a small-scale laboratory high shear mixer (Micromixer).

Citalopram base was sieved through a sieve aperture of 0.3 mm. The ingredients of the intragranular phase (1 - 4 in Table 1) were mixed at 600 rpm. 25 ml of purified water (5) was added in 30 sec and the granulation terminated after a total processing time of 3 min. The granulate was wet sieved through a 0.7 mm sieve aperture and dried at 40 °C in 30 minutes to equilibrium relative humidity of 32 %. The dried granulate was finally sieved through a 0.7 mm sieve aperture.

The dried granulate was mixed for 3 minutes with the extragranular phase (6 – 7) in a Turbula mixer and finally mixed with the lubricant (8) for 30 sec.

	Materials	%
1	Citalopram (base)	16.00
2	Kollidon VA64	2.32
3	Lactose 350 mesh	38.98
4	Corn starch	20.00
5	Purified water	25
6	Avicel PH 200 (Microcrystalline cellulose)	20.00
7	Ac-Di-Sol (Croscarmelose sodium)	2.00
8	Magnesium stearate	0.7

Table 1. Composition of the tablets.

Tablets were produced on a single punch tabletting machine Korsch EK0. The characteristics of the tables are shown in Table 2.

Parameter	Values
Tablet strength, mg	20
Nominal tablet weight, mg	125
Tablet diameter, mm	7
Tablet shape	Film coating (special doomed)
Mean disintegration time, min	1.77
Mean chrushing strength, N	69.1
Mean tablet weight, mg	125.4
RSD tablet weight, %	0.42
Friability, %	0.3

Table 2. Tablet characteristics.

The tablets produced had satisfactory technical properties.

Example 4

Melt granulation

The batch size was 200 g. Citalopram base was sieved through a sieve aperture of 0.3 mm. The granulation was performed in a small-scale laboratory high shear mixer (Micromixer)

The ingredients of the intra-granular phase (1 - 3 in Table 3) were mixed at 1200 rpm. The jacket temperature was 80 °C. The granulation process was terminated after 3.5 min. The granulate was sieved through a sieve aperture of 1.0 mm and mixed with the extra-granular phase (4, 5) for 3 min. and with the lubricant (6) for 30 sec.

	Materials	%
1	Citalopram (base)	16.00
2	Polyethyleneglycol 6000	9.14
3	Lactose 350 mesh	38.98
4	Avicel PH 200 (Microcrystalline cellulose)	30.00
5	Kollidon CL (Cross-linked povidone)	4.00
6	Magnesium stearate	0.7

Table 3. Composition of the tablet.

Tablets were produced on a single punch tabletting machine Korsch EK0. The characteristics of the tables are shown in Table 4.

Parameter	Values
Tablet strength, 20 mg	20
Nominel tablet weight, mg	125
Tablet diameter, mm	7
Tablet shape	Film coating , Special doomed
Mean disintegration time, min	1.0
Mean chrushing strength, N	55.5
Mean tablet weight, mg	125.6
RSD tablet weight, %	0.5
Friability, %	0.4

Table 4. Tablet characteristics.

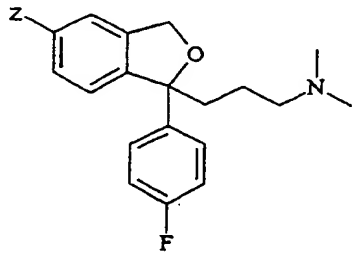
The tablets produced had satisfactory technical properties.

CLAIMS

1. A process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt thereof.

2. The process of Claim 1 for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or a crude mixture of citalopram.

3. A process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



(II)

wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, -CHO, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.

4. The process according to Claim 3 wherein the crude mixture of citalopram containing the compound of formula II as an impurity, is prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source.

5. The process according to Claim 3, wherein Z is halogen, in particular bromide or chloride.

6. The process according to Claims 3 to 5 wherein the crude mixture of citalopram is subjected to initial purification before the base of citalopram is precipitated in crystalline form.

7. The process according to Claims 3 to 5 wherein the crude mixture of citalopram is subjected to initial purification before a crude salt is formed from said crude mixture.

8. The process according to Claims 3 to 7 wherein the base of citalopram is set free from a crude salt or a crude mixture of citalopram by treatment with a base and optionally subjected to further purification before the base of citalopram is precipitated in crystalline form.

9. The process according to any of Claims 1 to 8 characterised in that the citalopram base is transferred into the hydrobromide or the hydrochloride salt of citalopram.

10. The process according to any of Claims 2-3, characterised in that the crude salt is a hydrobromide, hydrochloride, sulphate, oxalate, phosphate or nitrate salt, preferably the sulphate hydrobromide, or hydrochloride salt.

11. A crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram, characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

12. The crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram prepared by the process of any of Claims 1-10.

13. The base, the hydrochloride or the hydrobromide salt of claim 12 characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

14. A pharmaceutical composition containing the hydrochloride or the hydrobromide salt of citalopram according to Claims 11 to 13, or the crystalline base of citalopram.

15. A pharmaceutical composition according to Claim 14 which is a tablet prepared by

a) direct compression of citalopram, optionally in admixture with pharmaceutically acceptable adjuvants;

b) by compression of a wet granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants; or

c) by compression of a melt granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants.

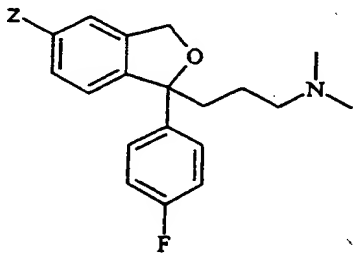
16. The pharmaceutical composition according to Claims 14 to 15 characterized in that it contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

Amendments to the claims have been filed as follows

1. A process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transformed into a salt thereof.

2. The process of Claim 1 for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or a crude mixture of citalopram.

3. A process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



(II)

wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, -CHO, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.

4. The process according to Claim 3 wherein the crude mixture of citalopram containing the compound of formula II as an impurity, is prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source.

5. The process according to Claim 3, wherein Z is a halogen, in particular bromide or chloride.

6. The process of Claim 5 wherein Z is bromide or chloride.

7. The process according to Claims 3 to 6 wherein the crude mixture of citalopram is subjected to purification before the base of citalopram is precipitated in crystalline form.

8. The process according to Claims 3 to 6 wherein the crude mixture of citalopram is subjected to purification before a crude salt is formed from said crude mixture.

9. The process according to Claims 3 to 8 wherein the base of citalopram is set free from a crude salt or a crude mixture of citalopram by treatment with a base and optionally subjected to further purification before the base of citalopram is precipitated in crystalline form.

10. The process according to any of Claims I to 9 characterised in that the citalopram base is transformed into the hydrobromide or the hydrochloride salt of citalopram.

11. The process according to any of Claims 2-3, characterised in that the crude salt is a hydrobromide, hydrochloride, sulphate, oxalate, phosphate or nitrate salt.

12. A crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram, characterised in that it has a purity of more than 99.8 %w/w.

13. The crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram prepared by the process of any of Claims 1-11.

14. The base, the hydrochloride or the hydrobromide salt of claim 13 characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

15. A pharmaceutical composition containing the hydrochloride or the hydrobromide salt of citalopram according to Claims 12 to 14, or the crystalline base of citalopram.

16. A pharmaceutical composition according to Claim 15 which is a tablet prepared by

a) direct compression of citalopram, optionally in admixture with pharmaceutically acceptable adjuvants;

b) by compression of a wet granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants; or

c) by compression of a melt granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants.

17. The pharmaceutical composition according to Claims 15 to 16 characterized in that it contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

Application No:	GB 0105982.3	**Examiner:**	S.I. AHMAD
Claims searched:	1-16	**Date of search:**	29 March 2001

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.S): C2C(CNB)

Int Cl (Ed.7): C07D-307/88

Other: DATA-BASE : CAS-ON-LINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	EP 0 347 066 H.Lundbeck (See Example 3)	1 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

HPLC purification (eluted with ethyl acetate / tetrahydrofuran 9:1 containing 4% of triethylamine) and by coll cting only the 5-10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0°C. The toluene solution was washed with water, dried ($MgSO_4$) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D$ = +11,81° (c = 1, CH_3OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ^1H NMR spectroscopy ($CDCL_3$ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (-)-1-(3-dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D$ = -12.34° (c = 1, CH_3OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.9%.

EXAMPLE 2

Resolution by methods b) and c)

To a solution of 85 gr of 4-(4-dimethylamino)-1-(4′-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile, hydrobromide in 500 ml of water were added 200 ml of ice cooled 2 M NaOH solution and 500 ml of ether. The mixture was stirred for 1/2 hour, the ether phase separated, dried ($MgSO_4$) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propanol at 40°C, and 40 gr of (+)-di-p-toloyltartaric acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipitated salt was filtered off and dried yielding 29.2 gr (55.1%) of (-)-4-(4-dimethylamino)-1-(4′fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, hemi (+)-di-p-toloyltartaric acid salt. MP: 134-135°C, $[\alpha]_D$ = +10.0° (c = 1, CH_3OH). The filtrate is used below.

To an ice cooled solution of 14 gr of the (-)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for 1/2 hour, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D$ = +12.33° (c = 1,CH_3OH).

The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D$ = +12.31° (c = 1, CH_3OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently colled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt, MP: 264-266°C, $[\alpha]_D$ = + 13.88°C (c = 1, dimethylformamide).

A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the following manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The waterphase was freeze-dried in vacuo (< 0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the (+)-4-(4-dimethylamino)-1-(4′-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, hemi (-)-di-(p-toloyl)tartaric acid salt ($[\alpha]_D$ = -8.9° (c = 1, CH_3OH)) which was converted to the corresponding diol base ($[\alpha]_D$ = +61.1° (c = 1, CH_3OH)) and finally ringclosure reaction yielded 10 gr of (-)-1-(d-dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D$ = -12.1° (c = 1, CH_3OH).

The oxalic acid salt of the (-)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D$ = -12.08° (c = 1, CH_3OH).

EXAMPLE 3

Pr paration of citalopram by method c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methansulfonyl chloride in 30 ml of dichloromethane wer added dropwise during ½ hour. The r action mixture was washed with 0.1 M NaOH solution twice, the organic phase separated, dried ($MgSO_4$) and the solv nt evaporated, leaving 21.5 gr of the titl (±)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184-186°C.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in development of 5-HT syndrome (Christensen, Fjalland, Pedersen, Danneskiold-Samsøe and Svendsen; European J. Pharmacol. 41, 153-162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and a 5-HTP is used as a reference for full 5-HT syndrome

The route of administration

30 minutes after the adminstration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5-10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: 1) excitation, 2) tremor, and 3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, ..., 9/9, where 0, 1, ..., 9 are the number of points per group after the dose in question. The ED_{50} value is calculated by log-probit analysis.

INHIBITION OF ^{3}H-SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of ^{3}H-serotonin (^{3}H-5-HT) (10 nM) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13-18; Hyttel, Prog.Neuro-Psychopharmacol. & Biol.Psychiat. 1982, 6, 277-295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146-153.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrified by decapitation and exsanguinated. Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogenizer) in 40 vol (w/v) of icecold 0.32 M of sucrose containing 1 mM of nialamide. The P_2 fraction (synaptosomal fraction) is obtained by centrifugation (600 g, 10 min and 25000 g, 55 min, 4°C) and suspended in 800 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

To 4000 µl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 µl test substance in water. After preincubation at 37° for 5 min, 100 µl of ^{3}H-1-NA (final concentration 10 nM) are added and the samples are incubated for 10 min at 37°C. The incubation is terminated by filtering the samples under vacuum through Whatman GF/F filters with a wash of 5 ml buffer containing 10 µM of unlab lled 5-HT. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) ar added. After shaking for 1 h and storag 2 h in th dark the content of radioactivity is